IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

DEY, L.P. and DEY, INC. Plaintiffs, v. SEPRACOR INC., Defendant.	C.A. No. 08-372-JJF

DECLARATION OF PRESTON K. RATLIFF II IN SUPPORT OF SEPRACOR'S OPENING BRIEF IN SUPPORT OF ITS MOTION TO DISMISS PURSUANT TO FED. R. CIV. P. 12(b)(1)

I, Preston K. Ratliff II, am associated with the law firm of Paul, Hastings, Janofsky & Walker LLP, counsel for Defendant, Sepracor Inc. ("Sepracor"). I make this declaration in support of SEPRACOR'S OPENING BRIEF IN SUPPORT OF ITS MOTION TO DISMISS PURSUANT TO FED. R. CIV. P. 12(b)(1).

1. Attached as Exhibit 1 hereto is a true and correct copy of a January 9, 2006 letter from Dey, L.P. to Sepracor.

2. Attached as Exhibit 2 hereto is a true and correct copy of excerpts from the transcript of the March 27, 2008 Markman hearing in the case *Sepracor Inc. v. Breath Ltd.*, C.A. No. 06-10043-DPW, in the United States District Court for the District of Massachusetts.

3. Attached as Exhibit 3 hereto is a true and correct copy of a May 1, 2008 Press Release of Sepracor Inc.

4. Attached as Exhibit 4 hereto is a true and correct copy of a document titled COVENANT NOT TO SUE REGARDING U.S. PATENT NO. 6,451,289 dated August 12, 2008.

5. Attached as Exhibit 5 hereto is a true and correct copy of the text of 21 C.F.R. § 314.94(a)(12)(viii)(A).

6. Attached as Exhibit 6 hereto is a true and correct copy of pages from a document titled RESPONSE OF CARACO PHARMACEUTICAL LABORATORIES, LTD. TO COMBINED PETITION FOR PANEL REHEARING AND REHEARING *EN BANC* OF APRIL 1, 2008 DECISION filed in Appeal no. 07-1404 in the United States Court of Appeals for the Federal Circuit.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: 8/13/08

Preston K. Ratliff II

CERTIFICATE OF SERVICE

I, hereby certify that on August 13, 2008, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing(s) to the following:

Steven J. Balick
John G. Day
Tiffany Geyer Lydon
ASHBY & GEDDES

I also certify that copies were caused to be served on August 13, 2008 upon the following in the manner indicated:

BY E-MAIL AND HAND DELIVERY

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/s/ Jack B. Blumenfeld
Jack B. Blumenfeld (#1014)

EXHIBIT 1

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL (707) 224-3200 FAX (707) 224-3235

January 9, 2006

Via Federal Express and Facsimile

President
Sepracor, Inc.
84 Waterford Drive
Malborough, Massachusetts 01752

Re: Notice of Paragraph IV Certification of levalbuterol HCl solution pursuant to the Federal Food, Drug and Cosmetic Act (21 USC § 355(j)(2)(A)(vii)(IV)), including the factual and legal basis for Dey, L.P.'s assertion of invalidity and/or non-infringement of U.S. Patent Nos. 5,362,755; 5,547,994; 5,760,090; 5,844,002; 6,083,993; and 6,451,289.

Dear Sir or Madam:

Dey L.P. ("Dey") has filed an Abbreviated New Drug Application (ANDA No. 77-800), pursuant to Section 355(j), Title 21, of the Federal Food, Drug & Cosmetic Act ("the Act") in order to obtain approval to engage in the commercial manufacture, use and sale of levalbuterol hydrochloride inhalation solutions ("Proposed Drug Products") currently sold under the established name, as defined in Section 502(u)(3) of the Act, "XOPENEX." The Proposed Drug Products will be aqueous, sterile, preservative-free inhalation solutions that comprise, inter alia, the active ingredient levalbuterol hydrochloride and will be manufactured and sold at three different dosage strengths: 0.36 mg levalbuterol hydrochloride (0.31 mg levalbuterol), 0.73 mg levalbuterol hydrochloride (0.63 mg levalbuterol), and 1.44 mg levalbuterol hydrochloride (1.25 mg levalbuterol).

According to the Food and Drug Administration Center for Drug Evaluation & Research Approved Drug Products With Therapeutic Equivalence Evaluations ("Orange Book") listings, XOPENEX, or treatment methods using XOPENEX, are claimed in U.S. Patent Nos. 5,362,755 ("the '755 Patent"), 5,547,994 ("the '994 Patent"), 5,760,090 ("the '090 Patent"), 5,844,002 ("the '002 Patent"), 6,083,993 ("the "993 Patent") and 6,451,289 ("the '289 Patent") (collectively, the "XOPENEX Patents"). Dey intends to manufacture and sell the Proposed Drug Products prior to the expiration of XOPENEX Patents which, according to the Orange Book, is November 8, 2011 for the '755 Patent, August 20, 2013 for the '994 Patent, January 5, 2010 for the '090 Patent, January 5, 2010 for the '002 Patent, January 5, 2010 for the '993 Patent, and March 21, 2021 for the '289 Patent.

It is Dey's position that the making, using, selling, offering to sell or importing of Dey's Proposed Drug Products would not infringe any valid claim of the XOPENEX Patents. It is Dey's position that all of the claims of the '755 Patent, '994 Patent, '090 Patent, '002 Patent, and '993 Patent (collectively, the "Barberich Patents") are invalid as anticipated and/or rendered obvious over the prior art. Further, at least certain claims of the Barberich Patents will not be infringed, either literally or under the doctrine of equivalents, by Dey's making, using, selling, offering to sell or importing its Proposed Drug Products. In addition, Dey's making, using, selling, offering to sell and importing of its Proposed Drug Products will not infringe any claim of the '289 Patent, either literally or under the doctrine of equivalents.

Accordingly, pursuant to Section 355(j)(2)(B)(i) and (ii) of the Act, we are hereby providing notice to Sepracor, owner of the above identified patents and the holder of the approved NDA No. 020837 for the FDA approved levalbuterol hydrochloride inhalation solutions sold under the tradename XOPENEX, that Dey has certified to the FDA, as required by 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that no valid claim of the XOPENEX Patents will be infringed

upon by the manufacture, use, sale, offer for sale or importation of the Proposed Drug Products. This letter ("Notice Letter") provides a detailed statement of the factual and legal bases for Dey's certification. This Notice Letter is provided without prejudice to Dey's raising other bases and/or defenses as to the validity, infringement and enforceability of this patent in the event of litigation and without waiver of any privilege or immunity against further disclosure.

I. SEPRACOR'S XOPENEX

Sepracor Inc.'s ("Sepracor") XOPENEX is supplied in 3 ml unit dose, low-density polyethylene (LDPE) vials as a clear, colorless, sterile, preservative-free, aqueous solution in three different strengths of levalbuterol (0.31 mg, 0.63 mg, and 1.25 mg, equivalent to 0.36 mg, 0.73 mg, and 1.44 mg of levalbuterol hydrochloride respectively).

According to Sepracor, treatment methods using XOPENEX are claimed in the Barberich Patents, which are summarized below:

Patent No.	Filing Date	Independent Claims (1)	Independent Claims (2)	Dependent Claims
5,362,755	12/7/93 (Listed by the USPTO as a continuation of 07/896,725 filed Jun. 9, 1992, which is a continuation of copending Application No. 07/461,262 filed on Jan. 5, 1990)	1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in	6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration or racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in	Claim 2-5 are dependent on claim 1. Claim 7 is dependent on claim 6.

Patent No.	Filing Date	Independent Claim (1)	Independent Claim (2)	Dependent Claims
		bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.	bronchodilation while simultaneously reducing undesirable side effects and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.	
5,547,994	11/7/94 (Listed by the PTO as a continuation of the '755 Patent)	1. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.	5. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.	Claims 2-4 are dependent on claim 1. Claim 6 is dependent on claim 5.

Patent No.	Filing Date	Independent Claim (1)	Independent Claim (2)	Dependent Claims
5,760,090	8/15/96 (Listed by the USPTO as a continuation of the '994 Patent)	1. A method of treating asthma, while reducing side effects associated with the administration of racemic albuterol, comprising administering to an individual suffering from asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.	NONE	Claims 2-9 are dependent on claim 1.
5,844,002	4/12/98 (Listed by the USPTO as a continuation of the '090 Patent)	1. A method of inducing bronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R-(-) albuterol sufficient to induce said bronchodilation.	10. A method of inducing bronchodilation or providing relief of bronchospasm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically pure R-(-) albuterol sufficient to induce said bronchodilation while simultaneously	Claims 2-9 are dependent on claim 1.

Patent No.	Filing Date	Independent Claim (1)	Independent Claim (2)	Dependent Claims
			reducing said adverse effects.	
6,083,993	12/17/99 (Listed by the USPTO as a continuation of the '002 Patent)	1. A method of treating bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(-) albuterol.	10. A method of preventing bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(-) albuterol.	Claims 2 to 9 are dependent on claim 1. Claims 11 to 17 are dependent on claim 10.
6,451,289	3/22/2001 (the USPTO did not disclose any data indicating the '289 Patent is related to any of the other patents).	2. A stable packaged preservative-free pharmaceutical formulation consisting essentially of: albuterol or a pharmaceutically acceptable salt thereof; sodium chloride; and water; said formulation having a pH of about 4, containing less than 0.08% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen, enclosed within an oxygen-permeable permeable plastic container, and remaining at less than 0.08% by weight of albuterol aldehyde after storage at	11. A preservative-free unit dosage formulation for administration by inhalation consisting essentially of: 0.18-1.4 mg albuterol or a pharmaceutically acceptable salt thereof; 27 mg sodium chloride; and 2-4 mL water; said unit dosage formulation having a pH of about 4, containing less than 1 ppm dissolved oxygen and containing less than 0.08% by weight of albuterol aldehyde after storage at 40.degree. C. for six months; wherein said unit dosage	Claim 1 is an independent claim directed to a method of manufacture. Claims 3 to 10 are dependent on claim 2. Claims 12 to 20 are formulations and methods manufactured according to claim 1.

Patent No.	Filing Date	Independent Claim (1)	Independent Claim (2)	Dependent Claims
		40.degree. C. for six months; wherein said formulation does not contain a chelating agent, a sequestering agent, an antioxidant, or a preservative.	formulation does not contain a chelating agent, a sequestering agent, an antioxidant, or a preservative.	Each claim expressly requires the absence of a "chelating agent".

According to the Orange Book, the exclusivity data for XOPENEX® includes an indication for treatment or prevention of bronchospasms in children six years of age and older with obstructive airway disease (I 347), which expires on January 30, 2005. The Patent Use Code for XOPENEX®, U 332, is defined as "Treatment Or Prevention Of Bronchospasms."

II. DEY'S PROPOSED DRUG PRODUCTS

The Proposed Drug Products will be aqueous, sterile, preservative-free inhalation solutions that comprise, *inter alia*, the active ingredient levalbuterol hydrochloride and will be manufactured and sold at three different dosage strengths: 0.36 mg levalbuterol hydrochloride (0.31 mg levalbuterol), 0.73 mg levalbuterol hydrochloride (0.63 mg levalbuterol), and 1.44 mg levalbuterol hydrochloride (1.25 mg levalbuterol). The inhalation solutions will be supplied in 3 ml unit dose, low-density polyethylene (LDPE) vials and will contain a chelating agent.

III. GENERAL STATEMENT OF THIS NOTIFICATION

In this Notice Letter, Dey asserts the following:

Prior art, including the GB '494 and GB '886 Patents,[1] anticipates and, either alone or in combination, renders obvious each claim of the Barberich Patents.

(2) Claims 4-5 of the '755 Patent, claim 4 of the '994 Patent, claims 5-9 of the '090 Patent, claims 5-9 of the '002 Patent, and claims 5-9 and claims 14-17 of the '993 Patent are not infringed, either literally or under the doctrine of equivalents, by the use, manufacture, sale or offering for sale of Dey's Proposed Drug Products.

Dey's Proposed Drug Products do not infringe, either literally or under the doctrine of equivalents, any of the claims of the '289 Patent.

IV. INVALIDITY

A. Anticipation

A patent is anticipated under 35 USC § 102(b) if "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." When considering the validity of a patented invention, each claim of the patent is considered separately. 35 USC § 282. If the invention claimed is described in a single prior art reference, the invention is anticipated if "'each and every limitation is found either expressly or inherently in a single prior art reference.'" *PIN/NIP, Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1243 (Fed. Cir. 2002) (citation omitted). A reference anticipates an invention if the reference discloses the claimed invention "'such that a skilled artisan could take its teachings in combination with his

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[1] GB '494 Patent refers to Great Britain Patent No. 1,298,494; GB '886 Patent refers to Great Britain Patent No. 1,200,886. Both of the GB '494 Patent and the GB '886 Patent were published more than one year prior to the filing date of any of the Barberich Patents and are therefore prior art under 35 U.S.C. § 102(b). The GB '494 Patent was not of record in the file histories of either the '755 or '994 Patents. Both the GB '494 and GB '886 Patents teach the treatment or prevention of asthma, bronchospasms and related conditions.

own knowledge of the particular art and be in possession of the invention.'." *In re Graves*, 69 F.3d 1147, 152 (Fed. Cir. 1995) (citing *In re LeGrice*, 301 F.2d 929, 936 (C.C.P.A. 1962)).

1. The GB '494 Patent Anticipates the Claims of the Barberich Patents.

The GB '494 Patent anticipates the claims in the Barberich Patents. For purposes of this analysis, claims 1, dependent claims 2-3, and claim 10 of the '002 Patent, provided below, are analyzed:[2]

> A method of inducing bronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R- (-) albuterol sufficient to induce said bronchodilation.
>
> A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.
>
> 3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.
>
> 10. A method of inducing bronchodilation or providing relief of bronchospasm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically pure R- (-) albuterol sufficient to induce said bronchodilation while simultaneously reducing said adverse effects.

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[2] Claims 1 and 10 of the '002 Patent are considered representative of each of the independent claims of the Barberich Patents and dependent claims 2-3 are considered representative of each of the dependent claims 2-3 of the Barberich Patents, therefore the analysis presented applies to the other correlated claims.

Each and every limitation of claims 1-3 and 10 of the '002 Patent are found either expressly or inherently in the GB '494 Patent. The GB '494 Patent teaches that the R(-) enantiomer is more active than the S(+) enantiomer in standardized tests for bronchodilation. Indeed, it teaches one of ordinary skill the art that an optically pure optical isomer of albuterol may be used to treat bronchodilation. Moreover, the optical rotation of the materials used was plus or minus 36.9 degrees, the same optical rotation as reported in earlier publication which some experts have indicated would be embraced by the definition of optically pure as defined in those patents.[3]

While claim 10 has the additional phrase "inducing bronchodilation while reducing the concomitant liability of adverse effects associated with racemic albuterol", the administration of an inhalation solution containing only the R( ) enantiomer would produce not only the bronchodilating effect described in the '494 Patent, but necessarily would do so without the side effects associated with the S(+) enantiomer. Merely reciting a reduction in side effects, which naturally and inherently occurs, does not render claim 10 and similar claims patentable.

As to the other dependent claims of the Barberich Patents, and, in particular, those claims relating to the route of administration or the dose, these claims are anticipated as well, with each and every limitation of the claims expressly or inherently disclosed by the 'GB '494 Patent.[4]

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[3] Even if the material in the GB '494 Patent is not as optically pure as the material claimed in the Barberich Patents, the GB '494 Patent still teaches one of ordinary skill in the art the use of optically pure isomers for the treatment of asthma, bronchospasms and related condition..

[4] The GB '494 Patent references the GB '886 Patent, therefore, for all of the reasons that the GB '886 Patent anticipates claims of the Barberich patents, the GB '494 Patent also anticipates those same claims of the Barberich patents.

2. The GB '886 Patent Anticipates the Claims in the Barberich Patents.

The GB '886 Patent (which was not of record during prosecution of any of the Barberich Patents) anticipates the claims identified above. The GB '886 Patent discloses that a class of compounds described therein have either stimulating or blocking actions on β-adrenergic receptors. One compound of specific focus is albuterol, which the GB '886 Patent specifically describes by name and indicates that it had been tested on asthmatic patients and found to provide equal speed of onset and longer action than a benchmark while providing lower effects on pulse rate and blood pressure. (See id. at 2, ll.10 17.) In addition, the reference notes that albuterol, when given orally, "has been found to be an effective bronchodilator in human beings after oral administration again without obvious cardiovascular actions." (Id., ll.18 19. The GB '886 Patent explains that the compounds were tested in anesthetized guinea pigs for the ability to relieve bronchial spasms induced by injection. (See id. at 4, ll.1 3. The patent also teaches that the compounds may be formulated for use in human or veterinary medicine, for therapeutic or prophylactic purposes. (See id. ll.46 47.) It describes dosage forms for administration of these materials as well as doses which may be provided. (See generally id. at 4, l.17 through 5, .14.) Examples 40 44 specifically describe dosage forms containing albuterol.

The GB '886 Patent also states:

> [a]s the compounds of general formula I possess at least one asymmetric carbon atom, the invention also includes all the possible optically active forms and racemic mixtures of the compounds. The racemic mixtures may be resolved by conventional methods, for example, by salt formation with an optically active acid, followed by fractional crystallization. Those

> compounds in which the side chain substituent is para to the phenolic hydroxyl group or para to the substituent X are preferred.

(*Id.* at 1, ll.29 34.) Albuterol falls within this preferred subclass and albuterol is the featured compound of the patent. Thus, the GB '886 Patent identifies albuterol as a preferred compound, provides evidence that it was successfully tested for the treatment of asthma, acknowledges that this specific compound is useful for the treatment of humans suffering from bronchospasms, and specifically acknowledges that it intended to encompass albuterol optical isomers (of which there are only two).

As to the dependent claims of the Barberich Patents, these claims are anticipated as well, with each and every limitation of the claims expressly or inherently disclosed by the 'GB '494 Patent. In particular, the GB '886 Patent teaches a dosage range of 1-100 mg for oral dosing and 50-1000 µg for inhalation. (See GB '886 Patent at 5, ll.6 11.) This anticipates those claims of the Barberich Patents which recite dosages of 1-8 mg for oral and 30-90 ug for inhalation, including claims 4-5 of the '755 Patent, claim 4 of the '994 Patent, claims 4-9 of the '090 Patent, claims 4-9 of the '002 Patent and claims 4-9 and 14-17 of the '993 Patent.

B. Obviousness

Where a claimed invention is not identically shown in the prior art, the claims of an issued patent can be invalidated under 35 USC § 103 for obviousness based on the prior art. The statute provides that:

> A patent may not be obtained though the invention is not identically disclosed as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the matter in which the invention was made.

Unlike anticipation, obviousness can be established based on one reference or on a combination of references. "Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference." *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000).

The GB '494 and GB '886 Patents, either alone or in combination, render obvious the claims of the Barberich Patents.[5] The GB '886 Patent teaches treatment and prophylaxis. Therefore, it renders obvious not only claims 1 and 10 of the '993 Patent relating to treatment and prevention respectively, but also the chronic uses of claim 1 of the '755 Patent. As for efficacy and selection of the R( ) enantiomer over the S(+) enantiomer, the GB '494 Patent explicitly cites the benefits of the R(-) isomer in terms of higher activity. In addition, the GB '494 Patent provides the optical rotation of the used material, which appears to be "optically pure" as defined by the Barberich Patents. (*See id.*, 11.68 74.) The GB '886 Patent also teaches treating both "patients" and "human beings" for asthma and bronchodilation. The treatment of other conditions specified in the Barberich Patents would therefore be obvious as well.

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[5] There is a motivation or suggestion to combine the two references or to modify the teachings of the references. The GB '494 Patent references the GB '886 Patent. Furthermore, the GB '886 Patent describes the optical isomers of the compounds disclosed, which include albuterol. The dosage forms disclosed in each patent are identical and the R(-) isomer is disclosed as being 50 times more active than the S(+) isomer. (*Compare* Examples 41 44 of the GB '886 Patent with Examples 2-5 of the GB '494 Patent.) Furthermore, the GB '886 Patent describes treatment of patients with asthma and the treatment of humans undergoing bronchospasms. (See GB '886 Patent at 2.) Taken together, these British references teach substituting the optical isomers of the GB '494 Patent for the uses described in the GB '886 Patent.

The GB '494 Patent describes an R(-) optical isomer with an optical rotation of -36.9°. The purity of such material would be 90% or more. Thus, claims 2 and 3 of all of the Barberich Patents, and claims 11 and 12 of the '993 Patent would be obvious as well. Even if the recitation of the optical rotation in the GB '494 Patent did not establish a purity of 90%, claims reciting that level of purity are, in this case, obvious. Knowing that the R(-) optical isomer is the most active, and knowing that the art taught separating the isomers to a relatively high purity and the separate administration of these isomers, it would have been obvious to one of ordinary skill in the art to provide the highest level of purity possible. Both patents teach, suggest, and motivate those of ordinary skill in the art to use optically pure R(-) optical isomer and one of ordinary skill in the art would have known how to make optical isomers of albuterol of the purities claimed.

Certain claims of the Barberich Patents (for example claims 5-6 of the '994 Patent and claims 5-6 of the '755 Patent) include claims relating to the administration of the R(-) enantiomer along with a drug selected from the group consisting of bronchodilators, antihistamines and analgesics. In a dependent claim, the analgesics are defined as aspirin, acetaminophen, and ibuprofen. It is noted, however, that dosage forms including albuterol and antihistamines were described in the art (see U.S. Patent No. 4,444,772 col.7, ll.57 61) and the use of aspirin in conjunction with albuterol was also known (see European Patent No. EP 0,248,150). Since the active ingredient of albuterol and levalbuterol are the same, it would be obvious to one or ordinary skill in the art to co administer levalbuterol with an antihistamine analgesic. Accordingly, claims 5 and 6 of the '994 Patent and claims 6 and 7 of the '755 Patent are obvious.

All of the remaining dependent claims of the Barberich Patents relate to the route of administration; either inhalation or oral (such as pill or syrup) and/or the appropriate doses to be given based on the route selected. Such additional limitations are very well known drug forms

and dosing regimens and would be obvious to one of ordinary skill in art. In fact, both of the British patents, expressly teach dosage forms for both oral administration and inhalation. (See, for example, the GB '494 Patent, Example 2 (tablets), Example 3 (aerosol formulations); see also GB '494 Patent, Examples. 3 5; p. 2, ll.27, 38 41; GB '886 Patent, Examples. 42 44; p. 2, ll.10 17; p. 4, ll.55 56; p 5, ll.1 2, 9 11.) In addition, the GB '886 teaches that for oral routes, β-adrenergic stimulants (such as albuterol) should be given at a dose of from 1-100 mg while the Barberich Patents claim oral administration of about 1 to about 8 mg and that, for aerosol doses using a metering valve, the metered amount of each dose should be "of the order of 50 -1000 µg." (GB '886 Patent at 5, ll.9 11.).

C. Secondary Considerations

To rebut a prime facia case of obviousness, the patent holder could present evidence of secondary considerations, including commercial success, long felt but unsolved need, failure of others, etc. Graham v. John Deere, 383 U.S. at 18. The patent holder bears the burden of establishing this objective evidence and showing that a nexus exists between the claimed features of the invention and the objective evidence offered to show nonobviousness. *Kandenberg v. Dairy Equip. Co.*, 740 F.2d 1560, 1567 (Fed. Cir. 1984). *See also Sandt Tech., Ltd. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1355 (Fed. Cir. 2001). In the event that the patent holder relies upon evidence of secondary considerations to rebut a *prima facie* case of obviousness, Dey intends to produce expert testimony to rebut that evidence.

V. NON-INFRINGEMENT OF THE BARBERICH AND THE '289 PATENTS

Dey's proposed levalbuterol product would not infringe any claim of the '289 Patent or certain claims of the Barberich Patents, either literally or under the doctrine of equivalents

A. Literal Infringement

To literally infringe a claim contained within a U.S. patent, the accused product or process must claim embody "every element of the claim." *Builders Concrete, Inc. v. Bremerton Concrete Prods. Co.*, 757 F.2d 255, 257 (Fed. Cir. 1985). Omission of even one element in the combination of elements recited in a patent claim avoids literal infringement of the claim. *See Hughes Aircraft Co. v. United States*, 140 F.3d 1470 (Fed. Cir. 1998).

B. Infringement Under the Doctrine of Equivalents

Where literal infringement cannot be established because one or more of the elements of a claim may not be literally met, it is possible that the claim may still be infringed under the doctrine of equivalents. *See Warner Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997); *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605 (1950). Infringement under the doctrine of equivalents requires a determination that each element in the accused embodiment performs substantially the same function in substantially the same way to obtain substantially the same result. *Dawn Equip. Co. v. Kentucky Farms Inc.*, 140 F.2d 1009, 1016 (Fed. Cir. 1998). The doctrine of equivalents is intended to reach those who make "unimportant and insubstantial changes and substitutions in the patent" that add nothing to the invention, but serve only to evade the literal scope of the claim language. *Graver Tank*, 339 U.S. at 607.

Accordingly, Dey's product does not infringe, either literally or under the doctrine of equivalents: claims 4- of the '755 Patent, claim 4 of the '994 Patent, claims 5 9 of the '090 Patent, claims 5 9 of the '002 Patent, 5- and 14-7 of the '993 Patent, or any claim of the '289 Patent.

C. The Barberich Patents

1 Non-Infringement of the Barberich Patents (Literal Infringement)

Claim 4 of the '755 Patent, claim 4 of the '994 Patent, claim 5 of the '090 Patent, claim 5 of the '002 Patent and claims 5 and 14 of the '993 Patent require that the R(-) albuterol be

administered by inhalation "in an amount of about 30 µg to about 90 µg." In contrast, the prescribing label for Dey's proposed levalbuterol product indicates that the smallest dose is 310 µg (.31 mg), almost four fold greater than the highest claimed dose. Accordingly, Dey's proposed levalbuterol product would not literally infringe claims 4 of the '755 Patent, claim 4 of the '994 Patent, claims 5 of the '090 Patent, claim 5 of the '002 Patent, and claims 5 and 14 of the '993 Patent.

Claim 5 of the '755 Patent, claims 6 9 of the '090 Patent, claims 6 9 of the '002 Patent, and claims 6 9 and 15 17 of the '993 Patent require that the R(-) albuterol be administered "orally." Dey's product will be administered by inhalation. Accordingly, Dey's proposed generic levalbuterol product would not induce literal infringement of claim 5 of the '755 Patent, claims 6- of the '090 Patent, claims 6- of the '002 Patent, and claims 6- and 15-7 of the '993 Patent.

2. Non-Infringement of the Barberich Patents (Doctrine Of Equivalents)

It is also Dey's position that Dey's proposed levalbuterol product would not infringe claim 4 of the '755 Patent, claim 4 of the '994 Patent, claim 5 of the '090 Patent, claim 5 of the '002 Patent and claims 5 and 14 of the '993 Patent under the doctrine of equivalents. As noted above, claim 4 of the '755 Patent, claim 4 of the '994 Patent, claim 5 of the '090 Patent, claim 5 of the '002 Patent, and claims 5 and 14 of the '993 Patent require that the R(-) albuterol be administered by inhalation "in an amount of about 30 µg to about 90 µg." In contrast, Dey's proposed levalbuterol product would be administered in no less than a dose of 310 µg.

The Federal Circuit has held that allowing an upper range limitation to cover a value four fold greater would eviscerate the plain meaning of that limitation, particularly where that limitation was shown to be critical. *See Conopco*, 46 F.3d at 1562 (citing *Pennwalt Corp. v. Durand Wayland, Inc.*, 833 F.2d 931, 935 (Fed. Cir. 1987) (en banc)). Similarly, allowing

"about 90 µg" to cover a dosage of 310 µg would eviscerate the plain meaning of the term, particularly where the Barberich Patents state that administration of 90 µg of R(-) albuterol will achieve the desired result (bronchodilation) in most patients. (*E.g.*, '755 Patent col.2, ll.54 56.) Accordingly, administration of Dey's proposed levalbuterol product as labeled would not infringe claim 4 of the '755 Patent, claim 4 of the '994 Patent, claim 5 of the '090 Patent, claim 5 of the '002 Patent and claims 5 and 14 of the '993 Patent under the doctrine of equivalents.

Similarly, claim 5 of the '755 Patent, claims 6 9 of the '090 Patent, claims 6 9 of the '002 Patent, and claims 6-9and 15-7 of the '993 Patent require that the R(-) albuterol be administered "orally." A treatment using oral administration (*e.g.*, a tablet or syrup) may not be equivalent to a method of treating using asthma using inhalation administration. Under the "function way result" equivalency test, a tablet or syrup does not function in the same way (absorption through the intestine) as an aerosol (absorption through the lungs). This is acknowledged by the Barberich Patents, which note that about 30 µg to about 90 µg of levalbuterol administered by inhalation one or more times a day should be sufficient to produce the desired bronchodilation effect, whereas for oral administration (*e.g.*, tablet or syrup), a dose of about mg to about 8 mg (an 11 to 267 fold increase) administered two to four times a day is sufficient.

D. The '289 Patent

1. Non-Infringement of the '289 Patent (Literal Infringement)

Dey's proposed product would not literally infringe the '289 Patent. Each of the claims of the '289 Patent require that the albuterol formulations and methods of manufacture "be[] free of chelating agents, sequestering agents, antioxidants, and preservatives." "Free" is defined as "not united with, attached to, or combined with something else." *Webster's New Collegiate Dictionary 453* (1981). Nothing in the '289 Patent or its prosecution history indicates that "free" was used other than in accordance with its ordinary meaning. In contrast, Dey's proposed

levalbuterol product will contain a chelating agent. Accordingly, Dey's product would not literally infringe any claim of the '289 Patent.

2. Non-Infringement of the '289 Patent (Doctrine Of Equivalents)

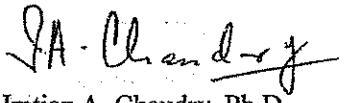
Dey's proposed levalbuterol product would not any infringe any claim of the '289 Patent under the doctrine of equivalents. As noted above, the claims of the '289 Patent require that the albuterol formulations and methods of manufacture "be[] free of chelating agents, sequestering agents, antioxidants, and preservatives." In contrast, Dey's proposed levalbuterol product will contain a chelating agent. Allowing the claims of the '289 Patent to cover such a product would vitiate an essential claim limitation, namely that there be no chelating agents, sequestering agents, antioxidants, and preservatives present in the albuterol formulation. *See Moore U.S.A., Inc. v. Standard Register Co.*, 229 F.3d 1091, 115 n.5 (Fed. Cir. 2000) ("The presence of a feature in an accused device . . . cannot possibly be equivalent to the claimed absence of that feature, and no reasonable fact finder could conclude otherwise."); *see also Warner Jenkinson*, 520 U.S. at 17, 39 n.8 (1997); *Durel*, 256 F.3d at 1305; *Tronzo*, 156 F.3d at 1160.

Furthermore, Sepracor would be estopped from asserting that Dey's proposed levalbuterol product infringed any claim of the '289 Patent under the doctrine of equivalents. The prosecution history indicates that Sepracor gave up albuterol formulations containing a chelating agent to procure issuance of the claims of the '289 Patent. Accordingly, Sepracor would be estopped from asserting that a formulation containing a chelating agent (such as Dey's proposed product) could possibly infringe. *See Pharmacia & Upjohn Co. v. Mylan Pharms., Inc.*, 170 F.3d 1373, 1377 (Fed. Cir. 1999); *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722 (2002); *see also Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Col, Ltd.*, 344 F.3d 1359 (Fed. Cir. 2003) (*en banc*).

VI. CONCLUSION

In summary, the claims of the five Barberich Patents are invalid as anticipated or obvious in view of the prior art discussed extensively herein. In addition, certain claims of these patents would not be infringed by the manufacture, use, sale, offer for sale or importation into this country of Dey's proposed levalbuterol product. In addition, Dey's proposed levalbuterol product will not infringe any claim of the '289 Patent.

Sincerely,



Imtiaz A. Chaudry, Ph.D.
Senior Vice President
Scientific Affairs

EXHIBIT 2

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

SEPRACOR, INC.	:	DOCKET NUMBER CA06-10043
PLAINTIFF	:	
versus	:	UNITED STATES COURTHOUSE
BREATH LIMITED	:	
DEFENDANT	:	BOSTON, MASSACHUSETTS

MARCH 27, 2008
9:00 a.m.

TRANSCRIPT OF MARKMAN HEARING

BEFORE: THE HONORABLE DOUGLAS P. WOODLOCK
UNITED STATES DISTRICT JUDGE

APPEARANCES:

ATTORNEYS FOR THE PLAINTIFF:

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PROCEEDINGS REPORTED USING MACHINE STENOGRAPHY.
TRANSCRIPT PRODUCED EMPLOYING COMPUTER-AIDED TECHNOLOGY.

Judge Skinner, who used to say that it should be a little bit like a Yankee meal, served cold and sliced thin, and this set of excrescencies, which I've commented on before, in connection with Discovery, serves nobody's purpose and, perhaps, may be counterproductive.

I don't see in the discovery motions anything that needs to be addressed before we get to the Markman matters, but, perhaps, counsel feel differently.

Do you?

Is there anything that has to be reached there?

MR. O'MALLEY: I agree with that, Your Honor.

Joe O'Malley, for the plaintiffs.

THE COURT: Okay.

Alright.

MR. FIGG: Tony Figg, for Breath.

We agree, Your Honor, unless you have questions.

THE COURT: No.

I do want to get to it at the end, but not now, so, I guess, you know, we start at the beginning and go to the end, with respect to these several matters.

I'm not sure I need to hear very much more on the question of whether the introductory phrase, "while reducing side effects associated with chronic administration of racemic albuterol," is a claim limitation, or similar language.

I do view it as a claim limitation. I don't view

it as a customary preamble.

The label, "preamble," seems to me to be not particularly helpful in this setting, but the short of it is I do view it as a claim limitation, and, so, I guess what I want to do is focus on the specifics of construction of the several disputed matters here and, I guess, start with the question of reducing side effects associated with chronic administration of racemic albuterol.

Do you want to go first, Mr. O'Malley?

MR. O'MALLEY: Certainly, Your Honor.

Will we be addressing this one patent at a time?

In other words, after the --

THE COURT: No, I think, language at a time, because it really seems to me to be interrelated.

MR. O'MALLEY: Alright.

THE COURT: Unless you want to make a somewhat different argument about how they are not to be read in a consistent fashion.

MR. O'MALLEY: That's fine, Your Honor.

Would you prefer I --

THE COURT: Wherever you're most comfortable.

MR. O'MALLEY: Okay. Let me stand at the podium, because I'm a bit tall.

THE COURT: Okay.

MR. O'MALLEY: We prepared some PowerPoints I can

and advantageous results that are indicative of unobviousness, but they do not add anything to the claim, and the reason they don't, Your Honor -- and I know this is a claim construction hearing -- but the point in the Bristol-Myers case was: You're simply claiming a method that was already in the prior art, and the simple observation that there are some characteristics or results from that method that weren't previously appreciated does not make the method patentable.

They said it's not a new use.

THE COURT: Anything else besides Bristol-Myers Squibb?

Anything else?

MR. FIGG: Well, I think the case law -- I think the case law is consistent that, with Bristol-Myers Squibb, that, when language in the claim does not define the way the method is performed, but, instead, defines a result to be achieved with the method, it should not be treated as a claim limitation.

THE COURT: Okay. I think I've heard sufficiently, so, as to that, I view it as a limitation, so let's move on to the construction phase.

MR. O'MALLEY: Okay.

Thank you, Your Honor.

Let's go to my slide, please, M-46.

(M-46 was displayed on the monitor.)

EXHIBIT 3

Press Release

Sepracor Announces Final Settlement of XOPENEX(R) Inhalation Solution Patent Infringement Litigation with Breath Limited

MARLBOROUGH, Mass.--(BUSINESS WIRE)--May 1, 2008--Sepracor Inc. (Nasdaq: SEPR) today announced that it has entered into a Settlement and License Agreement with Breath Limited (Breath), an Arrow Group subsidiary, to resolve the patent litigation involving Sepracor's XOPENEX(R) brand levalbuterol HCl Inhalation Solution products (1.25 mg/3 mL, 0.63 mg/3 mL and 0.31 mg/3 mL). The agreement permits Breath to launch generic versions of these XOPENEX Inhalation Solution dosages under terms of an exclusive license commencing on August 20, 2012. Upon launch, Breath would pay Sepracor a double-digit royalty on gross profits generated from the sales of generic versions of these XOPENEX Inhalation Solution dosages. The parties will promptly file a dismissal without prejudice in the United States District Court for the District of Massachusetts that will conclude this litigation.

Sepracor and Breath also contemporaneously entered into a Supply Agreement whereby, effective August 20, 2012, Sepracor will exclusively supply levalbuterol HCl products (1.25 mg/3 mL, 0.63 mg/3 mL and 0.31 mg/3 mL) to Breath, under Sepracor's New Drug Application (NDA), for a period of 180 days and on a non-exclusive basis for a period of time thereafter. In addition to the royalties described above, Breath will pay Sepracor on a cost plus margin basis for supply of the levalbuterol HCl products. Both the exclusive license under the Settlement and License Agreement and the exclusive supply obligations under the Supply Agreement could become effective prior to August 20, 2012 if a third party launches a generic version of those dosages of XOPENEX Inhalation Solution or if the parties otherwise mutually agree.

"We are very pleased to have reached a resolution of our dispute with Breath, which allows both parties to avoid the uncertainties and significant expenses related to complex patent litigation," said Adrian Adams, President and Chief Executive Officer of Sepracor Inc. "With this lawsuit behind us, Sepracor can continue to focus on leveraging the many opportunities that lay ahead with respect to our current product portfolio and our growing research and development pipeline, in addition to our efforts directed toward achieving success with the recently launched OMNARIS(TM) Nasal Spray product and the expected launch of ALVESCO(R) Inhalation Aerosol later this year."

"We are very pleased to be able to settle this matter," said Ian McAffer, Managing Director of Breath Limited. "This settlement will provide us with the certainty of being in a position to introduce versions of the XOPENEX Inhalation Solution products on a date certain without the burden of litigation."

The settlement agreement is a final settlement of the Breath litigation. The settlement with Breath does not end all disputes related to generic XOPENEX Inhalation Solution products, as litigation against Dey L.P. and Barr Laboratories, Inc. remains pending. In compliance with U.S. law, the Settlement and License Agreement and Supply Agreement will be submitted to the U.S. Federal Trade Commission and Department of Justice and are subject to their review.

About Sepracor

Sepracor Inc. is a research-based pharmaceutical company dedicated to treating and preventing human disease by discovering, developing and commercializing innovative pharmaceutical products that are directed toward serving unmet medical needs. Sepracor's drug development program has yielded a portfolio of pharmaceutical products and candidates with a focus on respiratory and central nervous system disorders. Currently marketed products include LUNESTA(R) brand eszopiclone,

XOPENEX(R) brand levalbuterol HCl Inhalation Solution, XOPENEX HFA(R) brand levalbuterol tartrate Inhalation Aerosol, BROVANA(R) brand arformoterol tartrate Inhalation Solution and OMNARIS(TM) brand ciclesonide Nasal Spray. Sepracor's corporate headquarters are located in Marlborough, Massachusetts.

Forward-Looking Statement

This news release contains forward-looking statements that involve risks and uncertainties, including statements with respect to the timing of introduction of generic versions of XOPENEX Inhalation Solution; Sepracor leveraging opportunities with respect to its current product portfolio and its growing research and development pipeline; achieving success with OMNARIS Nasal Spray; and the expected launch of ALVESCO Inhalation Aerosol later this year. Among the factors that could cause actual results to differ materially from those indicated by such forward-looking statements are: Sepracor's ability to fund, and the results of, further clinical trials with respect to products under development; the timing and success of submission, acceptance, and approval of regulatory filings; the scope of Sepracor's trademarks, patents and the patents of others and the success of challenges by others of Sepracor's patents; the clinical benefits and commercial success of the company's products; Sepracor's ability to realize the benefits of its sales force realignment and to expand its sales force capacity to accommodate the launches of OMNARIS Nasal Spray and ALVESCO Inhalation Aerosol; the ability of the company to attract and retain qualified personnel; the ability of the company to successfully collaborate with third parties; the performance of Sepracor's licensees and other collaboration partners; and certain other factors that may affect future operating results that are detailed in Sepracor's annual report on Form 10-K for the year ended December 31, 2007 filed with the Securities and Exchange Commission.

In addition, the statements in this press release represent Sepracor's expectations and beliefs as of the date of this press release. Sepracor anticipates that subsequent events and developments may cause these expectations and beliefs to change. However, while Sepracor may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing Sepracor's expectations or beliefs as of any date subsequent to the date of this press release.

For a copy of this release or any recent release, visit Sepracor's web site at www.sepracor.com.

CONTACT: Sepracor Inc.
David P. Southwell
Chief Financial Officer
or
Investor Relations
Jonae R. Barnes, 508-481-6700
Sr. Vice President

SOURCE: Sepracor Inc.

"Safe Harbor" Statement under the Private Securities Litigation Reform Act of 1995: Statements in this press release regarding Sepracor Inc.'s business which are not historical facts are "forward-looking statements" that involve risks and uncertainties. For a discussion of such risks and uncertainties, which could cause actual results to differ from those contained in the forward-looking statements, see "Risk Factors" in the Company's Annual Report or Form 10-K for the most recently ended fiscal year.

EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

DEY, L.P. and DEY, INC. Plaintiffs, v. SEPRACOR INC., Defendant.	C.A. No. 08-372-JJF

COVENANT NOT TO SUE REGARDING U.S. PATENT NO. 6,451,289

WHEREAS, Sepracor Inc. ("Sepracor") owns all rights, title and interest in U.S. Patent No. 6,451,289 (the "'289 patent");

WHEREAS, Dey, L.P. and Dey, Inc. (collectively "Dey") submitted abbreviated new drug application ("ANDA") Nos. 77-800 and 78-309 to the United States Food and Drug Administration for 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL, and 1.25 mg/0.5 mL strengths of levalbuterol hydrochloride inhalation solutions;

WHEREAS, Dey filed this civil action, captioned *Dey, L.P. and Dey, Inc. v. Sepracor Inc.*, C.A. No. 08-372-JJF on June 20, 2008, alleging that the products described in Dey's ANDA No. 77-800 do not infringe the '289 patent;

WHEREAS, pursuant to a confidentiality agreement in another lawsuit, *Sepracor Inc. v. Dey, L.P., et al.*, C.A. No. 06-113-JJF, Dey produced to Sepracor portions of Dey's ANDA No. 77-800 as pages numbered DLEV000001 – DLEV000037 and ANDA No. 78-309 as pages DLEV008918 – DLEV008945.

NOW, THEREFORE, Sepracor represents, stipulates, agrees and covenants as follows:

1. Sepracor unconditionally represents, stipulates, agrees and covenants that it will not sue Dey for infringement of, or otherwise assert, enforce, or hold Dey liable for infringement of the '289 patent based on the importation, manufacture, use, sale, or offer for sale of the levalbuterol hydrochloride inhalation solution products that are the subject of and described in Dey's ANDA No. 77-800, as produced to Sepracor as pages labeled DLEV000001 – DLEV000037, or Dey's ANDA No. 78-309, as produced to Sepracor as pages labeled DLEV008918 – DLEV008945.

2. This covenant has no bearing upon whether Dey's filing of ANDA Nos. 77-800 or 78-309, or the importation, manufacture, use, sale, or offer for sale of the levalbuterol hydrochloride inhalation solution products that are the subject of and described in Dey's ANDA Nos. 77-800 or 78-309 infringes any claim of the '289 patent.

3. This covenant has no bearing upon the validity or enforceability of any claim of the '289 patent.

Dated: August 12, 2008

SEPRACOR INC.

By: _____
Andrew I. Koven,
Executive Vice President, General Counsel and Corporate Secretary

EXHIBIT 5

has an active ingredient different from the reference listed drug:

(A) The drug product may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted under § 314.94; or

(B) The petition does not contain information to show that the different active ingredient of the drug product is of the same pharmacological or therapeutic class as the ingredient of the reference listed drug that is to be changed and that the drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use in the listed drug's labeling for which the applicant seeks approval; or

(C) The different active ingredient is not an active ingredient in a listed drug or a drug that meets the requirements of section 201(p) of the act; or

(D) The remaining active ingredients are not identical to those of the listed combination drug; or

(iv) Any of the proposed changes from the listed drug would jeopardize the safe or effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or effectiveness problem; or

(v) FDA has determined that the reference listed drug has been withdrawn from sale for safety or effectiveness reasons under § 314.161, or the reference listed drug has been voluntarily withdrawn from sale and the agency has not determined whether the withdrawal is for safety or effectiveness reasons.

(2) For purposes of this paragraph, ''investigations must be conducted'' means that information derived from animal or clinical studies is necessary to show that the drug product is safe or effective. Such information may be contained in published or unpublished reports.

(3) If FDA approves a petition submitted under this section, the agency's response may describe what additional information, if any, will be required to support an abbreviated new drug application for the drug product. FDA may, at any time during the course of its review of an abbreviated new drug application, request additional information required to evaluate the change approved under the petition.

(f) FDA may withdraw approval of a petition if the agency receives any information demonstrating that the petition no longer satisfies the conditions under paragraph (e) of this section.

§ 314.94 Content and format of an abbreviated application.

Abbreviated applications are required to be submitted in the form and contain the information required under this section. Three copies of the application are required, an archival copy, a review copy, and a field copy. FDA will maintain guidance documents on the format and content of applications to assist applicants in their preparation.

(a) *Abbreviated new drug applications.* Except as provided in paragraph (b) of this section, the applicant shall submit a complete archival copy of the abbreviated new drug application that includes the following:

(1) *Application form.* The applicant shall submit a completed and signed application form that contains the information described under § 314.50(a)(1), (a)(3), (a)(4), and (a)(5). The applicant shall state whether the submission is an abbreviated application under this section or a supplement to an abbreviated application under § 314.97.

(2) *Table of contents.* the archival copy of the abbreviated new drug application is required to contain a table of contents that shows the volume number and page number of the contents of the submission.

(3) *Basis for abbreviated new drug application submission.* An abbreviated new drug application must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected by the agency as the reference standard for conducting bioequivalence testing. The application shall contain:

(i) The name of the reference listed drug, including its dosage form and strength. For an abbreviated new drug application based on an approverd petition under § 10.30 of this chapter or § 314.93, the reference listed drug must be the same as the listed drug approved in the petition.

(ii) A statement as to whether, according to the information published in

the list, the reference listed drug is entitled to a period of marketing exclusivity under section 505(j)(4)(D) of the act.

(iii) For an abbreviated new drug application based on an approved petition under §10.30 of this chapter or §314.93, a reference to FDA-assigned docket number for the petition and a copy of FDA's correspondence approving the petition.

(4) *Conditions of use.* (i) A statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the reference listed drug.

(ii) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(5) *Active ingredients.* (i) For a single-active-ingredient drug product, information to show that the active ingredient is the same as that of the reference single-active-ingredient listed drug, as follows:

(A) A statement that the active ingredient of the proposed drug product is the same as that of the reference listed drug.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(ii) For a combination drug product, information to show that the active ingredients are the same as those of the reference listed drug except for any different active ingredient that has been the subject of an approved petition, as follows:

(A) A statement that the active ingredients of the proposed drug product are the same as those of the reference listed drug, or if one of the active ingredients differs from one of the active ingredients of the reference listed drug and the abbreviated application is submitted under the approval of a petition under §314.93 to vary such active ingredient, information to show that the other active ingredients of the drug product are the same as the other active ingredients of the reference listed drug, information to show that the different active ingredient is an active ingredient of another listed drug or of a drug that does not meet the definition of ''new drug'' in section 201(p) of the act, and such other information about the different active ingredient that FDA may require.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(6) *Route of administration, dosage form, and strength.* (i) Information to show that the route of administration, dosage form, and strength of the drug product are the same as those of the reference listed drug except for any differences that have been the subject of an approved petition, as follows:

(A) A statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the reference listed drug.

(B) A reference to the applicant's annotated proposed labeling and to the currently approved labeling for the reference listed drug provided under paragraph (a)(8) of this section.

(ii) If the route of administration, dosage form, or strength of the drug product differs from the reference listed drug and the abbreviated application is submitted under an approved petition under §314.93, such information about the different route of administration, dosage form, or strength that FDA may require.

(7) *Bioequivalence.* (i) Information that shows that the drug product is bioequivalent to the reference listed drug upon which the applicant relies; or

(ii) If the abbreviated new drug application is submitted under a petition approved under §314.93, the results of any bioavailability of bioequivalence testing required by the agency, or any other information required by the agency to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug. If the proposed drug product contains a different active ingredient than the reference listed drug,

FDA will consider the proposed drug product to have the same therapeutic effect as the reference listed drug if the applicant provides information demonstrating that:

(A) There is an adequate scientific basis for determining that substitution of the specific proposed dose of the different active ingredient for the dose of the member of the same pharmacological or therapeutic class in the reference listed drug will yield a resulting drug product whose safety and effectiveness have not been adversely affected.

(B) The unchanged active ingredients in the proposed drug product are bioequivalent to those in the reference listed drug.

(C) The different active ingredient in the proposed drug product is bioequivalent to an approved dosage form containing that ingredient and approved for the same indication as the proposed drug product or is bioequivalent to a drug product offered for that indication which does not meet the definition of ''new drug'' under section 201(p) of the act.

(iii) For each in vivo bioequivalence study contained in the abbreviated new drug application, a description of the analytical and statistical methods used in each study and a statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to the regulations under §56.104 or §56.105 of this chapter and that each study was conducted in compliance with the informed consent regulations in part 50 of this chapter.

(8) *Labeling*—(i) *Listed drug labeling.* A copy of the currently approved labeling (including, if applicable, any Medication Guide required under part 208 of this chapter) for the listed drug referred to in the abbreviated new drug application, if the abbreviated new drug application relies on a reference listed drug.

(ii) *Copies of proposed labeling.* Copies of the label and all labeling for the drug product including, if applicable, any Medication Guide required under part 208 of this chapter (4 copies of draft labeling or 12 copies of final printed labeling).

(iii) *Statement on proposed labeling.* A statement that the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) *Comparison of approved and proposed labeling.* A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under §314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

(9) *Chemistry, manufacturing, and controls.* (i) The information required under §314.50(d)(1), except that §314.50(d)(1)(ii)(*c*) shall contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product.

(ii) *Inactive ingredients.* Unless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant shall identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product.

(iii) *Inactive ingredient changes permitted in drug products intended for parenteral use.* Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

(iv) *Inactive ingredient changes permitted in drug products intended for ophthalmic or otic use.* Generally, a drug product intended for ophthalmic or otic use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product, except that, in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug, e.g., by using a balanced salt solution as a diluent as opposed to an isotonic saline solution, or by making a significant change in the pH or other change that may raise questions of irritability.

(v) *Inactive ingredient changes permitted in drug products intended for topical use.* Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an abbreviated application may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

(10) *Samples.* The information required under §314.50(e)(1) and (e)(2)(i). Samples need not be submitted until requested by FDA.

(11) *Other.* The information required under §314.50(g).

(12) *Patent certification*—(i) *Patents claiming drug, drug product, or method of use.* (A) Except as provided in paragraph (a)(12)(iv) of this section, a certification with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the reference listed drug or that claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the act and for which information is required to be filed under section 505(b) and (c) of the act and §314.53. For each such patent, the applicant shall provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(*1*) That the patent information has not been submitted to FDA. The applicant shall entitle such a certification ''Paragraph I Certification'';

(*2*) That the patent has expired. The applicant shall entitle such a certification ''Paragraph II Certification'';

(*3*) The date on which the patent will expire. The applicant shall entitle such a certification ''Paragraph III Certification''; or

(*4*) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the abbreviated application is submitted. The applicant shall entitle such a certification ''Paragraph IV Certification''. This certification shall be submitted in the following form:

I, (*name of applicant*), certify that Patent No. _____ (*is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of*) (*name of proposed drug product*) for which this application is submitted.

The certification shall be accompanied by a statement that the applicant will comply with the requirements under

§ 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under § 314.95(c) with respect to the content of the notice.

(B) If the abbreviated new drug application refers to a listed drug that is itself a licensed generic product of a patented drug first approved under section 505(b) of the act, the appropriate patent certification under paragraph (a)(12)(i) of this section with respect to each patent that claims the first-approved patented drug or that claims a use for such drug.

(ii) *No relevant patents.* If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (a)(12)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (*name of applicant*), there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug.

(iii) *Method of use patent.* (A) If patent information is submitted under section 505(b) or (c) of the act and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication that, according to the patent information submitted under section 505(b) or (c) of the act and § 314.53 or in the opinion of the applicant, is claimed by a use patent, an applicable certification under paragraph (a)(12)(i) of this section.

(iv) *Method of manufacturing patent.* An applicant is not required to make a certification with respect to any patent that claims only a method of manufacturing the listed drug.

(v) *Licensing agreements.* If the abbreviated new drug application is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, a certification under paragraph (a)(12)(i)(A)(*4*) of this section (''Paragraph IV Certification'') as to that patent and a statement that it has been granted a patent license.

(vi) *Late submission of patent information.* If a patent on the listed drug is issued and the holder of the approved application for the listed drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an abbreviated new drug application for that drug that contained an appropriate patent certification before the submission of the patent information is not required to submit an amended certification. An applicant whose abbreviated new drug application is submitted after a late submission of patent information, or whose pending abbreviated application was previously submitted but did not contain an appropriate patent certification at the time of the patent submission, shall submit a certification under paragraph (a)(12)(i) of this section or a statement under paragraph (a)(12)(iii) of this section as to that patent.

(vii) *Disputed patent information.* If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn or changed, the applicant shall submit an appropriate certification for each relevant patent.

(viii) *Amended certifications.* A certification submitted under paragraphs (a)(12)(i) through (a)(12)(iii) of this section may be amended at any time before the effective date of the approval of the application. However, an applicant who has submitted a paragraph IV patent certification may not change it to a paragraph III certification if a patent infringement suit has been filed against another paragraph IV applicant unless the agency has determined that no applicant is entitled to 180-day exclusivity or the patent expires before the lawsuit is resolved or expires after the suit is resolved but before the end of the 180-day exclusivity period. If an applicant with a pending application

voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. An applicant shall submit an amended certification by letter or as an amendment to a pending application or by letter to an approved application. Once an amendment or letter is submitted, the application will no longer be considered to contain the prior certification.

(A) *After finding of infringement.* An applicant who has submitted a certification under paragraph (a)(12)(i)(A)(*4*) of this section and is sued for patent infringement within 45 days of the receipt of notice sent under §314.95 shall amend the certification if a final judgment in the action against the applicant is entered finding the patent to be infringed. In the amended certification, the applicant shall certify under paragraph (a)(12)(i)(A)(*3*) of this section that the patent will expire on a specific date. Once an amendment or letter for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (a)(12)(i)(A)(*4*) of this section. If a final judgment finds the patent to be invalid and infringed, an amended certification is not required.

(B) *After removal of a patent from the list.* If a patent is removed from the list, any applicant with a pending application (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent shall amend its certification. The applicant shall certify under paragraph (a)(12)(ii) of this section that no patents described in paragraph (a)(12)(i) of this section claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents. In the amendment, the applicant shall state the reason for the change in certification (that the patent is or has been removed from the list). A patent that is the subject of a lawsuit under §314.107(c) shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended. An applicant shall submit an amended certification. Once an amendment or letter for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (a)(12)(i)(A)(4) of this section.

(C) *Other amendments.* (*1*) Except as provided in paragraphs (a)(12)(vi) and (a)(12)(viii)(C)(*2*) of this section, an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate.

(*2*) An applicant is not required to amend a submitted certification when information on a patent on the listed drug is submitted after the effective date of approval of the abbreviated application.

(13) *Financial certification or disclosure statement.* An abbreviated application shall contain a financial certification or disclosure statement as required by part 54 of this chapter.

(b) *Drug products subject to the Drug Efficacy Study Implementation (DESI) review.* If the abbreviated new drug application is for a duplicate of a drug product that is subject to FDA's DESI review (a review of drug products approved as safe between 1938 and 1962) or other DESI-like review and the drug product evaluated in the review is a listed drug, the applicant shall comply with the provisions of paragraph (a) of this section.

(c) [Reserved]

(d) *Format of an abbreviated application.* (1) The applicant must submit a complete archival copy of the abbreviated application as required under paragraphs (a) and (c) of this section. FDA will maintain the archival copy during the review of the application to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application, to give other agency personnel access to the application for official business, and to maintain in one place a complete copy of the application.

(i) *Format of submission.* An applicant may submit portions of the archival copy of the abbreviated application in

EXHIBIT 6

No. 07-1404

United States Court of Appeals for the Federal Circuit

CARACO PHARMACEUTICAL LABORATORIES, LTD.,
PLAINTIFF-APPELLANT

FOREST LABORATORIES, INC., FOREST LABORATORIES HOLDINGS, LTD., AND H. LUNDBECK A/S,
DEFENDANTS-APPELLEES

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF MICHIGAN IN NO. 3:07-CV-10737
JUDGE BERNARD A. FRIEDMAN

RESPONSE OF CARACO PHARMACEUTICAL LABORATORIES, LTD. TO COMBINED PETITION FOR PANEL REHEARING AND REHEARING *EN BANC* OF APRIL 1, 2008, DECISION

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filer loses, it must amend its Paragraph IV certification to a Paragraph III, thus losing its exclusivity as to that patent (at least under pre-MMA version of the Hatch-Waxman Act applicable here). *See* 21 C.F.R. § 314.94(a)(12)(viii)(A); *Mylan Pharm. Inc. v. Henney*, 94 F. Supp. 2d 36, 56-57 (D.D.C. 2000).[12] Thus, once the '712 patent expires, the only remaining barrier to Caraco's immediate market entry is Ivax's exclusivity on the '941 patent.

A ruling for Caraco on the '941 patent would trigger Ivax's exclusivity and allow Caraco to enter the market as soon as the '712 patent expires. If Caraco does not obtain a favorable ruling on the '941 patent, it can enter the market only 180 days after Ivax does so. A favorable ruling on the '941 patent is thus *guaranteed* to redress at least 180 days of market delay; and if Ivax were unable to enter the market when the '712 patent expired, it would redress much more. Thus, there is nothing speculative about Caraco's injury or a court's ability to redress it.

CONCLUSION

The petition for rehearing and rehearing *en banc* should be denied.

[12] In concluding that a subsequent ANDA filer could trigger Ivax's exclusivity only "by obtaining a judgment that *both* the '712 and '941 patents are invalid or not infringed," the Panel apparently overlooked the fact that Ivax lost its exclusivity on the '712 patent when it lost its challenge to that patent. Op. 11-12. This misstatement was unnecessary to the outcome, however, as the Panel rightly concluded that, even if Caraco needed to defeat the '712 patent, its injury was still concrete and redressable by a favorable ruling on the '941 patent. Op. 22-23.